

REMARKS

Claims 67-87 are pending in the present application and at issue. Claims 67 and 77 have been amended to address the indefiniteness rejection.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 67-87 under 35 U.S.C. 112

Claims 67-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Specifically, the Office stated that there is insufficient antecedent basis for the term "gene" recited in claim 67, lines 14-15 and objected to claim 77 for lacking "a positive process step in the method whereby a bacterial host cell is produced...."

Claims 67 and 77 have been amended as suggested by the Examiner. Applicants therefore submit that this rejection has been overcome.

II. The Rejection of Claims 67-69, 71-79, and 81-87 under 35 U.S.C. 102

Claims 67-69, 71-79, and 81-87 are rejected under 35 U.S.C. 102 as being anticipated by Rasmussen (US 2003/044940; entire document). This rejection is respectfully traversed.

Rasmussen discloses a method of increasing the number of copies of a gene of interest, wherein the gene of interest is contained within an "amplification unit". This is done by integrating the amplification unit into any location of the chromosome of a host cell, growing the host cell under conditions conducive for duplication of the amplification unit, and selecting a host cell comprising duplicated copies of the unit on the chromosome, whereby the gene of interest will also have been duplicated. The growth and selection steps may be repeated to achieve multiple duplication events, leading to an increasing number of copies of the gene of interest on the chromosome. Thus, the host cell produced by Rasmussen contains a number of copies of a gene of interest, which are located adjacent to each other on the genome of the cell.

However, Rasmussen do not disclose the methods of the present invention which involve a host cell comprising at least one copy of gene of interest integrated at one or more specific and well-defined locations on the genome, as claimed herein. For example, where a DNA construct comprising two non-functional conditionally essential genes and two copies of the gene of interest is introduced into the host cell, one copy of the gene of interest will integrate adjacent to and overlapping with one of the non-functional conditionally essential genes and the other copy of the

gene of interest will integrate adjacent to or overlapping with the other non-functional conditionally essential gene, which results in restoring the functionality of both conditionally essential genes, which renders the host cell selectable. Thus, the host cells of the present invention are patentably distinct from the host cells disclosed in Rasmussen.

The Office also states, that *"since the method of Rasmussen is drawn to a method of increasing the number of copies of the amplification unit in the chromosome of a host cell, the host cell must necessarily have a copy already present in the chromosome."* This is respectfully traversed.

The host cells disclosed in Rasmussen do not require a copy of the gene of interest before the first amplification unit is integrated in the first steps of the disclosed method. Thus, the methods disclosed in Rasmussen may increase the number of copies of the gene of interest from zero.

The Office also states that Rasmussen contemplates performing multiple cycles of the integration process in order to increase the copy number of the amplification unit/gene of interest, referring to paragraph [0031] on page 2, which reads:

"e) performing one or more cycles of steps c) and d) using the host cell selected in step d) in each new cycle; wherein the number of chromosomally integrated copies of the amplification unit increases with each cycle."

This is respectfully traversed.

The methods described in Rasmussen do not require more than one integration step. Once a copy of the amplification unit is integrated into the host cells of Rasmussen, additional copies are produced by tandem duplication events, and not by site-specific integration as in the instant invention.

The host cells in the methods of the present invention are required to have a copy of the gene of interest in the chromosome prior to integration of any additional copies, and following the integration of an additional copy of the gene of interest, the host cells are required to have at least two copies of the gene encoding the protein stably integrated into the chromosome in different positions, i.e., not as tandem-repeats such as resulting from the duplication of an amplification unit.

Thus, Rasmussen does not disclose the method of making host cells in the same manner as claimed in the instant application, and therefore it does not anticipate the invention as it regards making the cells and the cells themselves.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejections of Claims 67, 68, 71-78, and 81-86 under the Doctrine of Obviousness-Type Double Patenting

Claims 67, 68 and 71-76 are provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claim 59 in view of claims 1, 4, 16, 17 and 19 of co-pending Application No. 09/869,855 (Rasmussen). Claims 77, 78 and 81-86 are provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 16, 17 and 19 of co-pending Application No. 09/869,855. These rejections are respectfully traversed.

As discussed above, Rasmussen discloses and claims a method of increasing the number of copies of a gene of interest, wherein the gene of interest is contained within an "amplification unit". This is done by integrating the amplification unit into any location of the chromosome of a host cell, growing the host cell under conditions conducive for duplication of the amplification unit, and selecting a host cell comprising duplicated copies of the unit on the chromosome, whereby the gene of interest will also have been duplicated. The growth and selection steps may be repeated to achieve multiple duplication events, leading to an increasing number of copies of the gene of interest on the chromosome. Thus, the host cell produced by Rasmussen contains a number of copies of a gene of interest, which are located adjacent to each other on the genome of the cell.

In contrast, the methods of the present invention involve a host cell comprising at least one copy of a gene of interest integrated at one or more specific and well-defined locations on the genome. For example, where a DNA construct comprising two non-functional conditionally essential genes and two copies of the gene of interest is introduced into the host cell, one copy of the gene of interest will integrate adjacent to or overlapping with one of the non-functional conditionally essential genes and the other copy of the gene of interest will integrate adjacent to or overlapping with the other non-functional conditionally essential gene, which results in restoring the functionality of both conditionally essential genes, which renders the host cell selectable.

Thus, the host cells of the present invention are patentably distinct from the host cells disclosed in Rasmussen.

For the foregoing reasons, Applicants submit that the claims overcome these rejections under the doctrine of obviousness-type double patenting. Applicants respectfully request reconsideration and withdrawal of the rejections.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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